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Emerging ADCs and Combinations in TNBC

Announcer:
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Dr. Kalinsky:
Hi, this is Kevin Kalinsky. I'm a director of the Glenn Family Breast Center at Winship Cancer Institute in Atlanta, Georgia and I'll be talking about emerging antibody-drug conjugates and combinations in triple-negative breast cancer.

So, the first slide is just demonstrating the design of the TROPION-01 study, and I mentioned this briefly when talking about adverse events in antibody-drug conjugates. So this was a study that had different cohorts and the results of the triple-negative cohort now has been reported.

And you can see the antitumor response and what's notable here, one, this drug is given once every three weeks as opposed to two weeks and one week off, which is done with sacituzumab govitecan. And the response is notable at about a third of patients having a response. The other thing that's quite interesting is if you look at the asterisks. That highlights patients who had prior sacituzumab govitecan. And there are some patients who seem to respond and then some patients who had stable disease, and then others that had progressed.

We saw data from ESMO Breast about giving this drug, Plus Durvalumab. And these agents were given in combination once every three weeks until progressive disease. These were patients with frontline stage four triple-negative breast cancer with measurable disease and they were not allowed to have a prior checkpoint inhibitor or topoisomerase-based antibody drug conjugate, and the primary endpoint was safety and tolerability. You can see that there was a pretty remarkable response rate of about 74% of patients having a response. And you can also see that this included patients with high PD-L1 expression or low PD-L1 expressions demonstrated in purple. So there was some activity that was seen with this combination.

In terms of toxicities, there were low rates of diarrhea that were reported. There were no cases of interstitial lung disease or pneumonitis. There were patients who had stomatitis and this is a toxicity that we know even with single agent D-DXd. And even as this drug is being evaluated, there is prophylaxis that's being looked at for prevention of stomatitis. This shows HER2-Low breast cancer. And I just want to spend just a moment on this. And we'll see these results at ASCO at the plenary session, just demonstrating what we know by press release that for trastuzumab deruxtecan, which is approved for HER2-positive breast cancer, that there's also a benefit for patients who are HER2-Low, which is about 50% of patients with breast cancer.

You can see various designs that are being reported here. What we're going to be seeing are the results of DESTINY-04, but we are awaiting results of other studies including DESTINY-Breast06, which is trastuzumab deruxtecan versus physician choice chemotherapy, for patients with hormone receptor-positive HER2-negative disease or low disease. And those patients would be patients who were being treated in the frontline in terms of no prior chemotherapy. They must have had progression, tumor progression on endocrine therapy and as well as a CDK4/6 inhibitor. So if you go to the next slide, you can see the study that looked at the combination of T-DXd

plus Nivolumab, the checkpoint inhibitor. This was reported at ESMO Breast in the HER2-positive as well as the HER2-low cohorts.

And you can see the waterfall plot on the next curve for the patients who were HER2-positive as well as those that were HER2-low. And one of the notable things is that the response rate looks pretty similar to what you can see with single agent T-DXd. In terms of adverse events of special interest, there were some patients who agreed to ILD/Pneumonitis and there was one grade five patient as well.

This is just changing topics for just a moment, looking at a different antibody drug conjugate, Ladiratuzumab Vedotin, which is antibody drug conjugate that's targeting LIV1, and then also has MMAE as its payload, a single agent. You can see the response rate is about 25%. This study has been looking at different dosing schedules of Ladiratuzumab Vedotin. The primary toxicity that we can see with this particular ADC includes neutropenia as well as neuropathy.

One thing that is notable is the patients who received frontline, the combination of ladiratuzumab and immunotherapy, where there was a response rate of about a third. But this included patients who were PD-L1 negative and there are some additional patients that are being evaluated in this particular study, again, frontline PD-L1 negative, to look at the response rate in this enriched population.

And then I just want to end by talking about Patritumab Deruxtecan, which is a Novel Anti-3 ADC. Again, you can see the payload is exatecan derivative. And again, this is targeting HER3. And we have seen that HER3 can be expressed in multiple tumor types including breast, and there have been reports from a Phase 1/2 for patients with HER3-Positive breast cancer where we saw some nice responses across all the subtypes for HER2-Positive, hormone receptor-positive, HER2-Negative, and also for triple-negative breast cancer. And we will be seeing at San Antonio this coming weeks where we will get additional information just about activity as reported by ion crop.

So hopefully this gave a sense of the available antibody drug conjugates, as well as where things are going with the different TROP-2 antibody drug conjugates, also targeting of HER3, also targeting of LIV-1A. Hopefully, it's been clear that not all the ADCs are the same, that they have a different toxicity profile which may be due to the payload. Also, some studies looking in combination with checkpoint inhibition, in particular, D-DXd, that TROP-2 inhibitor that's given along with the checkpoint inhibitor frontline where we saw some really nice responses in the mid-seventies. Thank you so much for your attention. Appreciate it.

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